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| 08/813,781 | 03/07/1997 | JON A. WEIDANZ | 46745 | 3884 |

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| EXAMINER | |
|---|---|
| SCHWADRON, RONALD B | |

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| 1644 | 39 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 08/813,781 | Applicant(s) Weidanz et al. |
|---|---|---|
| | Examiner Ron Schwadron, Ph.D. | Art Unit 1644 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☐ Responsive to communication(s) filed on _____.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-4, 7-9, 13-15, 21-60, 62-64, 66-69, 71, and 72* is/are pending in the application.

4a) Of the above, claim(s) *3, 9, 13, 15, 21-60, 62-64, 66, and 68* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4, 7, 8, 14, 67, 69, 71, and 72* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. Claims 1, 2, 4, 7, 8, 14, 67, 69, 71, 72 are under examination as they read upon the elected species of TCR-bacteriophage coat protein fusion protein IE fusion protein comprising in sequence a V-α-peptide linker-Vβ-Cβ-bacteriophage coat VIII protein.

## RESPONSE TO APPLICANTS ARGUMENTS

2. The rejection of claims 1, 2, 4, 7, 8, 14, 67, 69, 71, 72 under 35 U.S.C. 103(a) as unpatentable over WO 96/18105 ( issued 13 June 1996) in view of Barbas US 5,759,817 ( filed Jan. 27, 1992), Onda et al. (Molecular Immunology 32:1387, 1995), and Huse et al. J. Immunology 149:3914, 1992 is with drawn in view of the 131 declaration filed Dec. 27, 1999 and the Card declaration filed 2/26/2001 which indicates that the construct disclosed in the 131 declaration filed Dec. 27, 1999 did contain a Cβ-fragment.

3. Claims 1, 2, 4, 7, 8, 14, 67, 69, 71, 72 stand rejected under 35 U.S.C. 103(a) as unpatentable over Chung et al. in view of Barbas US 5,759,817 ( filed Jan. 27, 1992), Onda et al. (Molecular Immunology 32:1387, 1995), and Huse et al. J. Immunology 149:3914, 1992 for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.

Chung et al. teaches a single chain T cell receptor which specifically binds to peptide ligand (see abstract). Chung et al. further teaches one embodiment of human single chain TCR in which C-terminus of V α domain is linked to N-terminus of V β chain via a 15 amino acid residue flexible amino acid liner and the C-terminus of the V β chain is linked to the beta chain constant domain (see Figure 1). In one embodiment the C terminus of V β chain is linked to a alkaline phosphatase (PI) protein tag ( see page 12655). Chung et also teach that the purpose of the linker is to enhance the binding characteristics of the soluble T cell receptor and that linkers of about 10 to 30 amino acid residues would be considered to be sufficient. Chung et al. teach that the TCR fusion protein can bind antigenic protein, thus teaching that the TCR fusion protein comprises an

antigen binding pocket. Chung et al. teaches a TCR fusion protein comprising V-α-peptide linker-V β-C β linked to GPI anchor and expression of such a fusion protein in a transfected eukaryotic cell ( see results section). Chung et al. disclose that the soluble form of TCR protein could be readily obtained by enzymatic cleavage with phosphatidylinostol-specific phospholipase C (PI-PLC) ( see page 12656). Chung et al. teaches expression of said TCR fusion protein in a bacterial cell system in which the N terminus of the Cβ region is linked to a histidine protein tag. Chung et al. also disclose a scTCR in which comprises V-α-peptide linker-V β-C β GPI in which the Cβ component consists of the β chain sequence ending right before the last cysteine (the sixth cysteine) ( see page 12655). Chung et al. further teach that TCR fusion proteins which do not contain the CB do not fold into the native conformation. The scTCR disclosed by Chung et al. meet the length limitations of the Vα. and Vβ region recited in claims 69 and 71. Chung et al. teach a soluble fusion protein comprising a Vα-peptide linker-Vβ-Cβ fragment-protein tag (eg. GPI). Chung et al. does not teach a TCR fusion protein further comprising bacteriophage VIII coat protein. However, Barbas discloses a soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a single-chain heterodimeric receptor ( see abstract and column 15, lines 27-28, in particular). Barbas also discloses that the fusion protein may comprise domains of heterodimeric proteins derived from several ligand binding proteins, including immunoglobulins and T cell receptors ( see column 17, lines 62-66 and column 19, lines, 9-28. Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable(V) and constant© region and T cell receptor has similarities in genetic organization and function to immunoglobulins ( see column 19, lines 19-22, in particular). Barbas also teaches that bacteriophage coat protein may be derived from cpIII or cpVIII ( see column 31, lines 10-28, in particular). Barbas discloses that expression vectors expressing soluble fusion proteins in which the ligand binding region is fused to bacteria coat protein allows the expression of the multiple fusion proteins on the surface of phage particles IE approximately 2700 cpVIII heterodimer receptor molecules per phage particle (see column 39 line 64 through column 40, line 7, in particular). Barbas further discloses that a short length of amino acid sequence at the amino end of a protein ( IE a protein tag) directs the protein to periplasmic space ( see column 8, lines 49-55, in particular. One embodiment of the invention is disclosed to be a fusion protein comprising in sequence a leader

sequence-peptide linker-V region amino acid residue-peptide linker -phage coat protein and that in one embodiment, the second linker can define a proteolytic cleavage site which allows the heterodimeric receptor to be cleaved from the bacteriophage coat protein to which it is attached (see column 14, lines 60-65). Onda et al .disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII ( see abstract and Figure 1, in particular). Onda et al. also teach that TCR-bacteriophage coat protein fusion protein can be used to study specific binding interactions of the TCR chain to antigenic ligands ( see paragraph bridging pages 1394-1395, in particular). Huse_et al. teach that fusion proteins comprising a single chain fusion protein comprising Fab fragment of immunoglobulin (which comprises the antigen binding pocket of the immunoglobulin molecule) and bacteriophage VIII coat protein can be produced and display the fusion protein when expressed in a M13 derived vector. Huse et al. further teach that bacteriophage VIII coat protein fusion protein can recovered from culture medium or from the periplasmic space (see abstract).

Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a soluble TCR fusion protein comprising the Vα.-peptide linker-Vβ -Cb fragment-protein taught by Chung et al. linked to a bacteriophage VIII coat protein because Barbas et al. and Onda et al. teach TCR-bacteriophage VIII coat fusion proteins can be used to study antigen binding properties of such a fusion protein and Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria and recovered in relatively large quantities. One with skill in the art would be motivated to make such a fusion protein to study the antigen binding region of the TCR component or to use the protein to elicit anti-idiotypic antibodies. One with skill in the art would be motivated to make such a fusion protein in which the Vα and Vβ region was derived from human TCR in order to study human TCR properties or to elicit anti-idiotypic antibodies to the TCR component of the protein.

Regarding applicants comments, while heterodimeric molecules are a preferred embodiment disclosed in Barbas et al., Barbas et al. disclose:
"In another embodiment, the present invention contemplates a polypeptide comprising an insert domain flanked by an amini-terminal secretion signal domain and a carboxy-terminal

filamentous phage coat protein membrane anchor domain. " (column 14, first complete paragraph).

Barbas et al. further disclose than said construct could include a "receptor protein" (column 14, second paragraph), indicating that the disclosed method could be used for receptors per se (eg. single chain or heterodimeric or single chain heteromers). Single chain T cell receptors were known in the art (see Chung et al.).

Regarding applicants comments about the single chain TCR taught by Chung et al., Chung et al. teach that the GPI anchor is cleaved and the soluble TCR still has all the antigen binding properties of the TCR (see pages 12656-12658). Thus, the GPI anchor is not required for the soluble TCR to function, it is just used in one particular method of making the soluble TCR. Regarding motivation to create the claimed invention, Chung et al. discloses that it would be desirable to produce their TCR in a phage display system (see page 12658, first column). In addition, Barbas et al. teach the advantages of their system for the production of peptides. Regarding reasonable expectation of success, both Barbas et al. and Chung et al. disclose use of phage display systems to produce single chain antibodies (see column 2, third paragraph from bottom and page 12658, first column). In addition, the soluble single chain TCR molecules functions with or without the GPI linker indicating that the construct itself is functional.

Regarding applicants comments about Holler et al., said publication was published in May 2000. In the amendment filed 6/3/2000, applicant submitted a publication by Weidanz et al. (J. Imm. Methods 1998) which discloses the claimed invention. Thus, it appears that Holler et al. simply are not familiar with the prior art. Thus, the comments of Holler et al. carry no weight because two years prior to the Holler et al. publication, Weidanz et al. had already published data regarding the production of single chain TCR using bacteriophage. Furthermore, Holler et al. discloses a yeast system for producing a single chain TCR and it appears that the main focus of Holler et al. is to promote their system. Regarding applicants comments about Onda et al ., the instant rejection indicates that "Onda et al. disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII ( see abstract and Figure 1, in particular)". The art recognizes that the alpha and beta chains of

the TCR generally both are involved in antigen binding. The art also recognizes that soluble TCR which bind antigen would have a variety of uses.

4. No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 308-4242.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644